1615

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 10/084,674	Confirmation No.	: 2545
Applicant	: JOHANNES BARTHOLOMAEUS, et al.		
Filed	: February 28, 2002		
TC/A.U.	: 1615		
Examiner	: Amy E. Pulliam		
Docket No.	: 029310.50986		
Customer No.	: 23911		
Title	: ORAL DOSAGE FORMS		

SUBMISSION OF DECLARATION UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Supplemental to applicant's reply of February 17, 2004, and in further support of applicant's arguments contained therein, submitted herewith is the Declaration Under 37 CFR § 1.132 of Dr. Johannes Bartholomaeus, the first-named inventor herein.

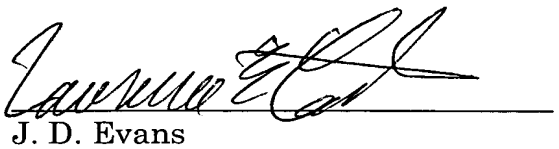
If there are any questions regarding the present submission or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and

please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #02931050986).

Respectfully submitted,

May 25, 2004



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Bartholomaeus et al.
Serial NO.: 10/084,674
FILED: 02/28/2002
FOR: ORAL DOSAGE FORMS

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Bartholomaeus, Johannes, hereby declare as follows:

1. I am a citizen of Germany, residing at In den Atzenbenden 54, D-52080 Aachen, Germany,

2. I studied pharmacy at the Technical University Carolo-Wilhelmina at Brunswick, Germany and received a PhD degree in pharmaceutical technology in the year 1988.

3. Since 1988 I have been working in the field of pharmaceutical technology for the company of Grünenthal GmbH at Aachen, Germany.

4. I am familiar with the US patent application Serial No. 10/084,674.

5. The following tests were made under my supervision and control:

Test I

150 g tramadol hydrochloride and 150 g microcrystalline cellulose (Avicel PH 101®, FMC) were homogenised and then granulated with an adequate quantity of demineralised water to obtain a granulate suitable for extrusion and spheronisation. The wet granulate was extruded by means of an extruder with a 1.0 x 2.0 mm extrusion template and the wet extrudate was spheronised in a spheroniser. The pellets were then dried for 24 hours at 50°C in the drying cabinet.

Application of the coating:

The pellets were coated in the fluidised bed with the aqueous dispersion of the composition described below with inlet-air temperature of 40°C up to a weight increase of 14% (relative to the starting weight of the pellets).

Aqueous dispersion:

Ethyl acrylate-methylmethacrylate-trimethyl ammonium ethylmethacrylate chloride copolymer with a ratio of monomers of 1:2:0.1 (30% aqueous dispersion, Eudragit RS30D®, Röhm)	625 g
Triethyl citrate	56 g
Polyethylene glycol 6000 (BASF)	5.3 g
Glycerine monostearate	3 g
Demineralised water	763 g

The release profile was determined of 451 mg of the coated pellets (content of tramadol hydrochloride: 200 mg) according to the method indicated in the description using the European Pharmacopoeia basket apparatus. Results obtained are set forth in the following Table 1:

Table 1

Time (minutes)	Tramadol hydrochloride released in mg
0	0
30	15
60	58
120	130
240	178
360	192
480	198

Test II

150 g tramadolsaccharinate and 150 g microcrystalline cellulose (Avicel PH 101®, FMC) were homogenised and then granulated with an adequate quantity of demineralised water to obtain a granulate suitable for extrusion and spheronisation. The wet granulate was extruded by means of an extruder with a 1.0 x 2.0 mm extrusion template and the wet extrudate was spheronised in a spheroniser. The pellets were then dried for 24 hours at 50°C in the drying cabinet.

Application of the coating:

The pellets were coated in the fluidised bed with the aqueous dispersion of the composition described below with inlet-air temperature of 40°C up to a weight increase of 14% (relative to the starting weight of the pellets).

Aqueous dispersion:

Ethyl acrylate-methylmethacrylate-trimethyl ammonium ethylmethacrylate chloride copolymer with a ratio of monomers of 1:2:0.1 (30% aqueous dispersion, Eudragit RS30D®, Röhm)	150 g
Triethyl citrate	4.5 g
Polyethylene glycol 6000 (BASF)	9 g
Glycerine monostearate	2.3 g
Demineralised water	134.2 g

The release profile was determined of 686 mg of the coated pellets (content of tramadolsaccharinate: 298 mg, equivalent to 200 mg tramadol hydrochloride) according to the method indicated in the description using the European Pharmacopoeia basket apparatus. Results obtained are set forth in the following Table 2:

Table 2

Time (minutes)	Tramadol released in mg (calculated as tramadol hydrochloride)
0	0
30	8
60	14
120	30
240	50
360	64
480	78
720	106

Test III

according to US patent application Serial No. 10/084,674.

50 g tramadol hydrochloride, 526 g tramadolsaccharinate and 384 g microcrystalline cellulose (Avicel PH 101®, FMC) were homogenised and then granulated with an adequate quantity of demineralised water to obtain a granulate suitable for extrusion and spheronisation. The wet granulate was extruded by means of an extruder with a 1.0 x 2.0 mm extrusion template and the wet extrudate was spheronised in a spheroniser. The pellets were then dried for 24 hours at 50°C in the drying cabinet.

Application of the coating:

The pellets were coated in the fluidised bed with the aqueous dispersion of the composition described below with inlet-air temperature of 40°C up to a weight increase of 14.4% (relative to the starting weight of the pellets).

Aqueous dispersion:

Ethyl acrylate-methylmethacrylate-trimethyl ammonium ethylmethacrylate chloride copolymer with a ratio of monomers of 1:2:0.1 (30% aqueous dispersion, Eudragit RS30D®, Röhm)	177 g
Triethyl citrate	5.3 g
Polyethylene glycol 6000 (BASF)	10.6 g
Glycerine monostearate	3.0 g
Demineralised water	164.1 g

The release profile was determined of 549 mg of the coated pellets (content of tramadol hydrochloride: 25 mg, content of tramadolsaccharinate: 298 mg, total amount of tramadol equivalent to 200 mg tramadol hydrochloride) according to the method indicated in the description using the European Pharmacopoeia basket apparatus. Results obtained are set forth in the following Table 3:

Table 3

Time (minutes)	Tramadol released in mg (calculated as tramadol hydrochloride)
0	0
30	18
60	39
120	54
240	72
360	85
480	98
720	126

IV. Results:

Test I and test II show that the release profile of tramadol hydrochloride respectively tramadolsaccharinate is different.

According to Test III a tramadol release profile different from that of Test I and of Test II is achieved, if the different salts of tramadol are present in the same dosage form.

Therefore, according to the invention as claimed in the US patent application Serial No. 10/084,674, it is possible to adjust the drug release profile by having different salts of the same active substance in one and the same formulation.

All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true, and further, these statements were made with the knowledge that willful false statements and the like, so made, are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent application or any patent issued thereon.

Aalen, April 30th, 2004 — (Date)

(Dr. Bartholomäus, Johannes)